REMARKS

Rejection of Claims and Traversal Thereof

In the March 4, 2010 Office Action:

Claims 1, 3, 5-7 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hancock (US Pub. No. 2002/0019345, hereinafter Hancock) in view of Baba, et al (Proc. Natl. Acad. Sci. USA, May 1999, vol. 96 pp. 5698-5703, hereinafter Baba); and

Claims 1, 3, 5-7 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Vezina (WO94/05300, hereinafter Vezina) in view of Baba.

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

Rejection under 35 U.S.C. §103(a)

1. Claims 1, 3, 5-7 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hancock in view of Baba and according to the Office, the combination of Hancock and Baba defeats the patentability of the presently claimed invention. Applicants insist that such a combination does not establish a *prima facie* case of obviousness.

Applicants' claimed invention is recited in claim 1 and a composition with three important elements:

1) at least one G1 phase arresting compound;
2) at least one HIV viral entry inhibitor that inhibits entry of HIV to mononuclear cells; and
3) the G1 phase arresting compound is in an amount sufficient to increase concentrations of extracellular β-chemokines, wherein the chemokines comprise MIP-1α, MIP-1β and RANTES.

Notably, the G1 phase arresting compound must be in an amount sufficient to increase the level of ß-chemokines including MIP-1α, MIP-1β and RANTES. The Office should be aware that any proposed combination of references must also provide guidance that such a composition has a sufficient amount of the G1 phase arresting compound to increase the level of extracellur ß-chemokines. None of the cited references, alone or in combination teach or suggest the expected result.

Hancock describes a composition that includes an antagonist of CCR5 and an immune suppressant, wherein the composition **is used to reduce graft rejections**. Hancock provides a broad and extensive list of possible antagonists that would be effective to react at the CCR5 receptor and used to reduce graft rejection, including a small organic molecule, natural product, protein, peptide or peptidomimetic.

Hancock is very concerned about an increase or continuous release of chemokines because they recruit more immune cells to the site of inflammation. To prevent this increase of chemokines the Hancock group includes an immunosuppressant to reduce the immune response. The list of immunosuppressive agents is set forth in paragraph 60 and includes a multiplicity of different choices, as shown below:

> **[0060]** The term "immunosuppressive agent", as used herein, refers to compounds which can inhibit an immune response. The immunosuppressive agent used in the invention can be a novel compound or can be selected from the compounds which are known in the art, for example, calcineurin inhibitors (e.g., cyclosporin A, FK-506), IL-2 signal transduction inhibitors (e.g., rapamycin), glucocorticoids (e.g., prednisone, dexamethasone, methylprednisolone, prednisolone), nucleic acid synthesis inhibitors (e.g., azathioprine, mercaptopurine, mycophenolic acid) and antibodies to lymphocytes or antigen-binding fragments thereof (e.g., OKT3, anti-IL2 receptor). Novel immunosuppressive agents can be identified by those of skill in the art using suitable methods, for example, screening compounds for the capacity to inhibit antigen-dependent T cell activation.
>
> **[0061]** The immunosuppressive agent used for co-therapy (e.g., co-administration with an antagonist of CCR5 function) is preferably a calcineurin inhibitor. More preferably the immunosuppressive agent used for co-therapy is cyclosporin A.

Specifically, the Hancock group administers the immunosuppressive agent to lower the level of chemokines and prefers the use of cyclosporin A to induce this result. Chemokines are considered to be pro-inflammatory compounds and Hancock requires the reduction of an immune response.

According to the Office:

> Hancock teach a method for inhibiting the rejection of transplanted grafts comprising an effective amount of an antagonist of CCR5 and an effective amount of an immunosuppressive agent (see abstract and claims 1, 6 and 13). Immunosuppressive agents include rapamycin (see paragraph 60; addresses claims 1 and 3). AND Hancock does not teach TAK 779 (claims 1, 5 and 6).
>
> Baba et al. teaches that TAK-779 is a small-molecule, nonpeptide that is a specific CCR5 antagonist (see title and abstract).
>
> To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the compositions of Hancock et al. and TAK 779 because TAK 779 is a small molecule that specifically antagonizes CCR5.

Thus, in order to overcome the shortcoming of Hancock, the Office, with the help of applicants' specification, introduced the Baba reference which describes the use of TAK 779 as a CCR5 antagonist. Then, the Office proposes that the teachings of these two disparate references render the presently claimed invention as obvious. Applicants disagree.

Baba provides for the use of a CCR5 antagonist that sits on the CCR5 receptor and inhibits binding of the HIV virus and stops the access of the virus to the receptor. However, it should be noted that Baba is attempting to treat HIV and certainly does not teach, suggest or desire the use of an immunosuppressant compound as taught by Hancock. Clearly, a reference that is attempting to stop the negative effects of HIV would never consider including an immunosuppressant compound such as that in Hancock. In fact, the exact opposite would be important because an HIV infected individual needs to maintain a healthy and active immune system. Applicants question how these two references are even combinable, noting that Baba seeks to maintain a healthy immune response, while in contrast Hancock seeks to suppress an immune response to stop any graft rejection.

According to the MPEP § 2143.01 V – VI:

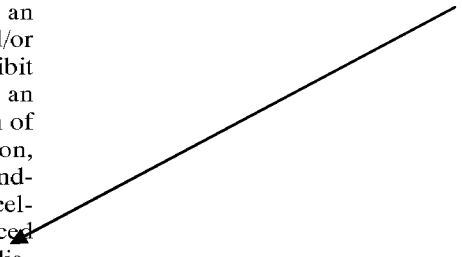
> "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. … [and] If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious."

Applicant submits that if the teachings of Hancock are combined with Baba, then the end result of Baba would be rendered unsatisfactory for its intended use, that being, treating HIV. According to the Court in *In re Gordon,* 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification and the Office has not established a *prima facie* case of obviousness.

Importantly, Baba seeks to maintain a healthy immune response to fight the HIV virus, whereas the addition of the Hancock composition with an immunosuppressant would defeat this purpose.

The Office's contention that Hancock teaches an effective amount of the G1 phase arresting agent to increase concentrations of extracellular beta-chemokines is not supported by the actual disclosure of Hancock. The Hancock reference only discusses a therapeutic effect that relates to stopping graft rejections. The mention of a therapeutic effect cannot be extended to increasing levels of chemokines especially when the Hancock reference provides for reducing immune responses. It is fundamental that the induction of chemokines is necessary for a healthy and normal immune response and chemokines are considered to be proinflammatory mediators. From paragraph [0068], recreated below, it is evident that Hancock is interested in inhibiting the induction of proinflammatory mediators which is the exact opposite as that of the present invention.

[0068] An "effective amount" of a CCR5 antagonist is an amount sufficient to achieve a desired therapeutic and/or prophylactic effect, such as an amount sufficient to inhibit graft rejection. For example, an effective amount is an amount sufficient to inhibit a (i.e., one or more) function of CCR5 (e.g., CCR5 ligand-induced leukocyte migration, CCR5 ligand-induced integrin activation, CCR5 ligand-induced transient increase in the concentration of intracellular free calcium $[Ca^{2+}]_i$ and/or CCR5 ligand-induced secretion (e.g., degranulation) of proinflammatory mediators), and thereby inhibit graft rejection. An "effective amount" of an additional therapeutic agent (e.g., immunosuppressive agent) is an amount sufficient to achieve a desired therapeutic and/or prophylactic effect (e.g., immunosuppression).



Thus, Hancock never envisioned increasing the levels of an immune response and the Office may not speculate on such an effect.

The Office's contention that it would be obvious to make a composition comprising a G1 phase arresting agent and an antiviral agent that increases levels of beta-chemokines is similar to an "obvious to try"

rejection. If this is the situation, it is important for the Office to review the "*In re Kubin*" ruling decided on April 3, 2009 because it provides guidance showing that the presently claimed invention is not obvious. (See I*n re Kubin*,90 USPQ2d 1417 (Fed. Cir. 2009))

Specifically, the *Kubin* Court revisited the *In re O'Farrell* decision (*In re O'Farrell*, 853 F.2d 894(Fed Cir. 1988)) and discussed that to differentiate between proper and improper applications of "obvious to try," the O'*Farrell* Court outlined two classes of situations where "obvious to try" is erroneously equated with obviousness under §103. In the first class of cases:

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

In such circumstances, wherein metaphorical darts would be thrown at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness.

The second class of *O'Farrell's* impermissible "obvious to try" situations occurs where

> what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Notably, the combined references provide no guidance for a treatment that both increases the level of chemokines and inhibits entry of HIV virus. Importantly, applicants' invention is not merely a composition including a G-1 phase arresting agent and HIV entry inhibitor, but instead is a novel and nonobvious composition that increases the level of chemokines and the positive immune response concomitant with such increase. No prior art suggests this and applicants insist that the cited references do not teach or suggest the increase of ß-chemokines.

Importantly applicants have provided proof of the effectiveness of the presently claimed combination that not only shows increased levels of chemokines but reduced levels of HIV virus. The proposed combination does not teach or suggest these benefits.

Initially it should be noted that the present invention provides for combination of a CCR5 antagonist and the G1 phase arresting agent wherein the G1 phase arresting agent must be in a sufficient amount to increase the level of chemokines and specifically the MIP-1α, MIP-1β and RANTES chemokines.

Applicants have surprisingly found that the addition of RAPA increases the level of chemokines as shown in Figure 3A, recreated below:

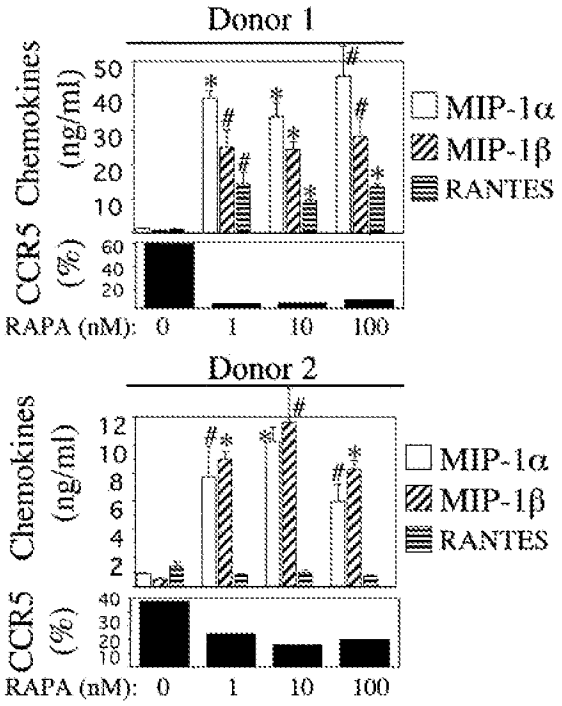


Figure 3A

As the Court stated in *Interconnect Planning Corp. v. Feil,* 227 USPQ 543 (Fed. Cir. 1985) "The invention must be viewed not with the blueprint drawn by the inventor, but **in the state of the art that existed at the time.**" (Emphasis added.) The state of the art existing at the time of the invention was characterized by understanding that combining a CCR5 antagonist and immunosuppressive agent caused a reduction of chemokines. Nothing in the combination hinted of an increase in chemokines. Moreover, there is no suggestion or teaching that this combination would effectively increase an immune response and reduce replication of HIV.

In light of the above discussion, applicants request reconsideration and the withdrawal of this rejection for obviousness.

2. Claims 1, 3, 5-7 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Vezina in view of Baba. Applicants insist that such a combination does not establish a *prima facie* case of obviousness.

According to the Office, Vezina, et al (WO 94/05300) teaches the use of RAPA and an antiviral HIV agent that in combination with Baba defeats the patentability of the presently claimed invention.

Applicants disagree because Vezina does not disclose teach or suggest the use of an antiviral agent **that inhibits entry of HIV into affected cells.** As previously stated, Vezina only teaches the use of **reverse transcriptase inhibitors or protease inhibitors**, both of which are not effective until the enemy has passed over the moat, into the castle, through the door, and has taken over the castle or ready to take over every castle in the kingdom. (Attacking every T-cell in the system).

One of the major effects of the Vezina reference is the loss of CD4+ cells because the cell replication is decreased. Vezina teaches that this loss of CD4 cells is acceptable; however, applicants know that the loss of CD4+ cells causes increased problems for patients infected with HIV because of the diminishment of immune response.

Reviewing the results of Example 2 of Vezina (reproduced below) shows the emphasis on the inhibition of CD4+ cell replication:

EXAMPLE 2.
In vitro incubation of rapamycin with CD4+ human cells uninfected and infected with defective HIV-1.

TEST CELL CULTURES:

Different concentrations of rapamycin were tested on the following cell lines in culture:
-MT-4 (CD4+ T lymphocytes);
-MT-2 (MT-4 cells infected with a defective HIV-1 HTLV III_B (Harada et al., Science 229: 563-566, 1985, enclosed herewith by reference);
-U937 (monocyte) (ATCC CRL-1593); and
-UHC8 (U937 infected with a defective HIV-1 HTLV III_B, R3 strain (Boulerice et al., J. Virol., 66, 1745-1755, 1990, enclosed herewith by reference).

It is evident from the results below that replication of infected cells CD4+ cells (MT-2 and UHC8) was inhibited, and thus, fewer T-cells are available to the immune system to combat the HIV virus. Clearly,

this is a problem because of the diminishment of immune T cells that are required to overcome the negative effects of HIV.

Results are presented in Table 3 as percent of inhibition of cellular growth of infected and uninfected host cells:

Table 3

Rapamycin (ng/ml)	MT-4 (% inhibition)	MT-2 (% inhibition)	U-937 (% inhibition)	UHC8 (% inhibition)
0	0	0	0	0
0.01	36	49	24	48
0.1	78	85	78	83
1	87	–	–	87
10	81	85	78	81
100	82	86	82	82

The toxicity of the compound at 100 ng/ml through 0.1 ng/ml was greater than about 80% cellular inhibition both for uninfected and infected cells. Although, at 0.01 ng/ml, the infected cells seemed slightly more sensitive to rapamycin than the uninfected cells, it seems that the anti-HIV effect of rapamycin may be due primarily to its toxicity on the replication of the host cells (lymphocytes and monocytes).

Thus, the replication of T cells is decreased and the subject can be depleted of an important soldier of the immune system.

In sharp contrast, the present invention avoids the shortcomings of Vezina because the CD4 containing T-cells are not reduced but the cell viability is maintained with an increase of chemokines which provides for the maintenance of the cell viability but also a reduction of HIV replication as shown in Figure 5 A.

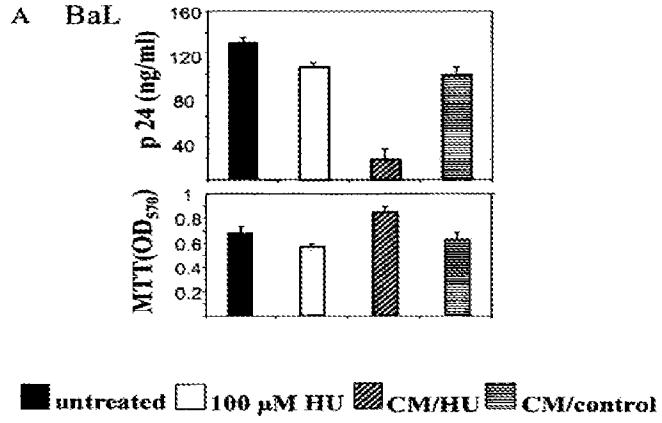


Figure 5

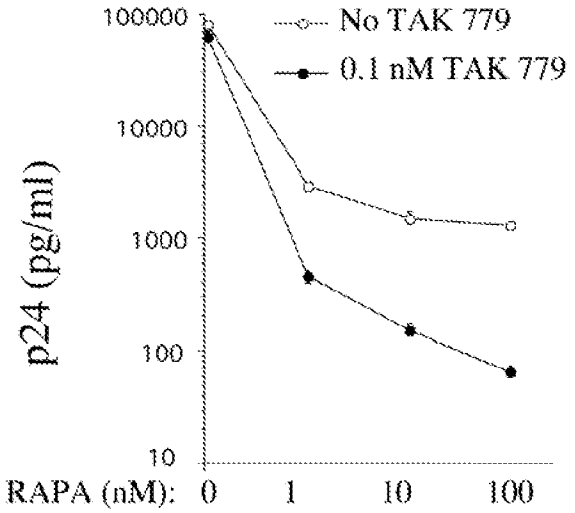
Figure 5 provides the results of using hydroxyurea as the G1 phase arresting agent. The antiviral activity of the supernatants collected from cultures of PBMCs that had been exposed to 100 μM HU for 7 days [supernatants referred to as conditioned medium (CM)] was evaluated in PBMCs infected with HIV-1 BaL and HIV-1 IIIb. Briefly, PHA-activated PBMCs were infected with each virus at 100 tissue culture 50% infective dose units ($TCID_{50}$)/10^6 PBMCs or 10 $TCID_{50}$/10^6 PBMCs for 2 h at 37°C. Infected cells were cultured in IL-2 medium alone, IL-2 medium with 100 μM HU, IL-2 medium containing 50% supernatant from HU-treated PBMCs (CM/HU), or IL-2 medium containing 50% supernatant from control-treated PBMCs (CM/control). On day 3 after infection, culture medium was replaced with fresh medium of the same kind as on day 1. Viral growth (measured by p24 levels in the supernatant) and cell viability (assayed by MTT) were determined on day 7 after infection.

It is evident that using the G1 phase arresting agent, hydroxyurea, maintained the cell viability including T cells and also reduced viral growth.

According to the Office, the Baba reference teaches the use of TAK 779 and proposes that it would be obvious to a skilled artisan to combine Vezina with Baba. Applicants insist that this general statement by the Office relating to HIV and pharmaceuticals is totally without merit. On logical grounds, given the possibility of adverse drug-drug interaction, the added constraint of dealing with different solubilities, bioavailability, biocompatibility, etc. and other practical difficulties of cocktail formulation, the *prima facie* obviousness of such approach is not at all evident as the "general proposition" put forward by the Office. Further, it is imperative that the Office recognizes that there are no working examples in Vezina that shows a combination of RAPA with an antiviral agent. All of the test in Vezina, administer the compounds separately and to separate test animals. In fact, the antiviral agent is used as a control in many of the tests. Therefore, the combination of drugs proposed by the Examiner has not in fact been shown to be effective in the treatment of HIV.

Clearly, applicants have shown improvement surpassing any results shown in Vezina or Baba. Applicants have provided proof of the effectiveness of the presently claimed combination that includes a G1 phase arresting agent in combination with an agent that stops the HIV virus before entry into the cell.

As shown in Figure 6 of the application, and recreated below for ease of discussion,



it is evident that there is a three-log reduction in viral replication with the combination of RAPA and TAK 779. Clearly, 0.1 nM TAK-779 shows little antiviral activity and the results shown in Figure 4 (as set forth in the specification) indicate that administering RAPA alone reduces the level of P24 to nanograms/ml amounts. However, the combination of both agents reduces the levels of p24 to picograms/ml. Thus, the combination provides for a surprising reduction in replication of HIV-1.

Notably, by using the G1 phase arresting agent in combination with an antiviral that prevents the introduction of the virus into the cell, the addition of extra chemokines that block the landing sites maintains the availability of the T-cell and reduce infections.

This efficacy is also shown in Figure 7 when hydroxyurea is combined with TAK 779 as shown below:

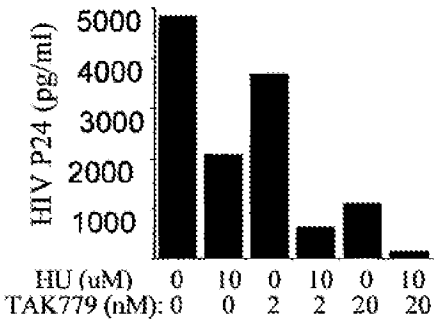


Figure 7

According to the Office, a skilled artisan would read the Baba reference and immediately disregard use of AZT of Vezina and instead use TAK 779 even if Vezina never shows the effectiveness of such combination. Applicants question where in either reference is there any suggestion that the proposed combination would be effective? There is none and the Office cannot speculation on such a combination, unless of course the Office is using applicants' specification as a blue print to go looking for ingredients. This type of hunting expedition would be using impermissible hindsight which is still considered unacceptable because the *KSR* Court expressly stated that a flexible TSM test remains the primary guarantor against **a non-statutory hindsight analysis such as the Office is using in the presently claimed invention.**

On July 21, 2008, the Federal Circuit expanded on post *KSR* establishment of a *prima facie* case of obviousness and stated in *Eisai Co. Ltd v Dr. Reddy Laboratories* 87 USPQ2d 1452 (Fed Cir 2008) that (1) *KSR* assumes a starting reference point, prior to the time of the invention, from which a skilled artisan might identify a problem and pursue potential solutions; (2) that the record up to the time of the invention would give some reason to make particular modifications; and (3) the record would provide some reason to narrow the prior art universe to a "finite number of identified and predictable solutions." Notably the *Eisai* Court further stated the "to the extent that an art is unpredictable, as in the chemical arts often are, *KSR's* focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable".

Applicants insist that after a review of the new guidelines for determination of obviousness and recent relevant case law, the Office cannot establish a *prima facie* case of obviousness and as such, applicants request that the rejection under 35 U.S.C. §103(a) be withdrawn.

Rejoinder of Method Claims

In accordance with Office guidelines recited in MPEP Section 821.04, when the elected product claims are found to recite patentable subject matter then the method claims that have been withdrawn may be rejoined and examined in this one application provided the method of use recite limitations corresponding to those found to be patentable during examination of the elected invention. As such, when the product claims are found to recite patentable subject matter, non-elected method claims 11, 12, 15-18, 23, 25, 27, 30, 33, 35, and 37-47 should be taken up for examination.

Petition for Extension and Fees Payable

Applicants petition for a two month extension of time, extending the June 4, 2010 deadline for response to August 4, 2010. The fee for such extension is being paid herewith by electronic transfer. If any additional fee is found due for entry of this response, the Commissioner is authorized to charge such fee to Deposit Account No. 13-4365 of Moore & Van Allen.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Carter reconsider the patentability of the pending claims in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. If any issues remain outstanding incident to the allowance of the application, Examiner Carter is requested to contact the undersigned attorney at (919) 286-8089.

Respectfully submitted,

/mariannefuierer/

Marianne Fuierer
Reg. No. 39,983
Attorney for Applicants

Moore & Van Allen, PLLC
Telephone: (919) 286-8000
Facsimile: (919) 286-8199